

## 1. SCIENTIFIC ABSTRACT

Carcinoma of the prostate is one of the most common tumors in the United States affecting 179,300 men this year. The disease increased markedly between 1989 and 1992 probably because earlier detection of early stage tumors was possible using the prostate-specific antigen (PSA) blood test. Prostate cancer is easily treated when it remains localized to the prostate, but can be difficult to treat once it has spread. Many tumors are responsive to anti-hormonal therapy, but when tumors become resistant to hormonal manipulation the disease is usually fatal. There will be an estimated 37,000 deaths this year from prostate cancer. The incidence and mortality have been disproportionately high in the African-American population. Thus, new modalities for treating or preventing prostate cancer are urgently needed.

The identification of antigens specific to prostate cells, such as PSA, generated interest in using these as targets for immune recognition. Preliminary studies revealed several T-cell specific epitopes within the PSA coding sequences, suggesting that vaccine strategies targeted to PSA may be possible. The human PSA gene has been cloned, sequenced, and inserted into vaccinia virus and fowlpox virus vectors for immunization. Preclinical studies established the safety and effectiveness of this approach in animal models using a PSA-expressing tumor model. These results have now been extended into advanced prostate cancer patients using the vaccinia-PSA vaccine in a phase I clinical trial. Although still early, results of this trial have found the vaccine safe and analysis of clinical and biochemical responses are on-going.

The optimal vectors for immunization against cancer are not known. Vaccinia virus is an attractive virus since it has an extensive history of safe administration in the human population and it elicits strong cytotoxic T-lymphocyte (CTL) responses. However, adequate immunization may be limited by strong neutralizing antibody titers against the virus upon subsequent boosting with vaccinia virus. Fowlpox virus is an avian pox virus that does not replicate in mammalian cells, thus reducing pathogenicity, but elicits strong CTL responses. Additionally, studies in mice have shown that heterologous prime and boosting with alternating vaccinia and fowlpox viruses led to more potent CTL and enhanced therapeutic effectiveness against established tumors. The use of prime and boost strategies using alternating poxvirus vectors has not been studied in prostate cancer patients to date.

This study proposes to evaluate the prime and boost strategy for vaccination against prostate cancer by randomizing patients with D0 prostate cancer into three arms. The first arm will receive a series of four fowlpox viruses expressing PSA every six weeks. The second cohort will receive a priming dose of vaccinia-PSA followed by three fowlpox-PSA vaccines. The third cohort will receive three fowlpox-PSA vaccines followed by a single vaccinia-PSA vaccine. Patients with D0 prostate cancer represent an earlier stage of metastatic disease when there is biochemical evidence of increased PSA by blood measurement, but limited (or no) evidence of tumor by radiologic assessment. These patients may be better able to mount an effective immune response against their cancer when compared to patients with bulky metastatic disease. This study will be conducted as a limited institution ECOG trial.